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Cardiovascular Risk and Risk Factor Management in Type 2 Diabetes: A Population-Based Cohort Study Assessing Sex Disparities

Running Title: *Wright et al.; Sex Disparity in Cardiovascular Risk & Management*

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Abstract

Background: With recent changes in UK clinical practice for diabetes care, contemporary estimates of sex disparities in cardiovascular risk and risk factor management are needed.

Methods: In this retrospective cohort study, using the Clinical Practice Research Datalink linked to hospital and death records for people in England, we identified 79,985 patients with incident T2DM between 2006-2013 matched to 386,547 patients without diabetes. Sex-stratified Cox models were used to assess cardiovascular risk.

Results: Compared to women without T2DM, women with T2DM had a higher cardiovascular event risk (adjusted HR 1.20 [95% CI 1.12-1.28]) with similar corresponding data in men (HR 1.12 [1.06-1.19]) leading to a non-significant higher relative risk in women (risk ratio 1.07 [0.98-1.17]). However, some important sex differences in the management of risk factors were observed. Compared to men with T2DM, women with T2DM were more likely to be obese, hypertensive and have hypercholesterolaemia but were less likely to be prescribed lipid-lowering medication and ACE inhibitors, especially if they had CVD.

Conclusions: Compared to men developing T2DM, women with T2DM do not have a significantly higher relative increase in cardiovascular risk, but ongoing sex disparities in prescribing should prompt heightened efforts to improve the standard and equity of diabetes care in women and men.



Key Words: sex-specific; cardiovascular disease risk factors; cardiovascular outcomes; type 2 diabetes mellitus; database

Circulation

Clinical Perspective

What is new?

- In contrast to earlier studies, in this large contemporary cohort we showed no significant gender disparities in CVD risk associated with the development of T2DM.
- Important sex differences in the management of risk factors remained: women with T2DM were more likely to be obese, have hypercholesterolemia and hypertension and were less likely to be prescribed statins and ACE inhibitors, especially if they had CVD.
- In T2DM subgroups with CVD, women were less likely to receive antiplatelet agents than men.

What are the clinical implications?

- The observed gender biases in risk factor management highlight the need for closer adherence to prescribing guidance, continued routine surveillance for gender-related prescribing biases and possibly greater uptake of professional-based interventions in the community supporting the provision of high-quality equitable care.
- Particular attention is required for women with abnormal cardiovascular risk factors, who may be receiving suboptimal preventative care.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in people with diabetes.^{1,2} Four large meta-analyses showed that after developing diabetes, the increase in the risk for fatal coronary heart disease, stroke or other atherosclerotic death was 27-50% higher for women than men.³⁻⁶ The mechanism behind this sex disparity is still unclear but growing evidence suggests that the development of type 2 diabetes (T2DM) could adversely affect metabolic and CVD risk factor profiles more in women than men.^{7,8} Some of the excess risk observed in women could be explained by suboptimal and less aggressive CVD risk factor management, particularly after acute myocardial infarction,⁷⁻¹² however, these previous studies lacked sufficient data to assess this.³⁻⁵



As the majority of studies examining sex disparities in CVD risk in diabetes are now over a decade old (1960-2005)³⁻⁵, these estimates may not be relevant for contemporary practice. With a UK pay-for-performance scheme (Quality and Outcomes Framework; QOF) introduced in general practice in 2004 to improve diabetes care, the recording and monitoring of disease management has greatly improved over time and this is likely to have contributed to the year-on-year reductions in risk for fatal and non-fatal CVD events.¹³⁻¹⁶

Our primary aim was to determine if sex disparities in CVD risk associated with T2DM are evident in a contemporary national cohort. Our secondary aim was to investigate the extent of any sex differences in the management of CVD risk factors and if these differences explain any disparities in CVD risk. Our hypotheses were that there would be no sex disparities in cardiovascular risk or risk factor management.

Methods

Ethical Approval

This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. ONS and HES data is subject to Crown copyright (2018) protection, re-used with the permission of The Health, & Social Care Information Centre, all rights reserved. The OPCS Classification of Interventions and Procedures, codes, terms and text is Crown copyright (2016) published by Health and Social Care Information Centre, also known as NHS Digital and licensed under the Open Government Licence available at www.nationalarchives.gov.uk/doc/open-government-licence/open-government-licence.htm. The interpretation and conclusions contained in this study are those of the authors alone. The study was approved by the Independent Scientific Advisory Committee (ISAC) for CPRD research, ref. 15_123Mn.

Data Sharing

Read and ICD codes used are publicly available at The ClinicalCodes repository¹⁷ and can be accessed at <https://clinicalcodes.rss.mhs.man.ac.uk/>. Electronic health records are, by definition, considered “sensitive” data in the UK by the Data Protection Act and cannot be shared via public deposition because of information governance restriction in place to protect patient confidentiality. Access to data is available only once approval has been obtained through the individual constituent entities controlling access to the data. The primary care data can be requested via application to the Clinical Practice Research Datalink (<https://www.cprd.com>); secondary care data can be requested via application to the hospital episode statistics from the UK Health and Social Care Information Centre (www.hscic.gov.uk/hesdata); and mortality data

are available by application to the UK Office for National Statistics (www.ons.gov.uk/ons/index.html).

Data Source

This retrospective population-based cohort study used data from the Clinical Practice Research Datalink (CPRD), an anonymised, longitudinal primary care medical record database of UK general practices.¹⁸ In 2015, the CPRD contained data on over 4.4 million active (alive, currently registered) patients from 674 registered general practices, equating to approximately 6.9% of the UK population.¹⁸ Patients are broadly representative of the general population in terms of age, sex, and ethnicity.¹⁸ The CPRD dataset was linked at the patient-level to hospitalisation data (Hospital Episode Statistics, HES), national mortality data (Office for National Statistics, ONS) and deprivation data, for all eligible patients in 380 linkage-consenting English practices. More detailed information on linkage is available in the Supplemental Methods.

Study Population

Incident T2DM cases were identified from Read codes in the electronic health record, if their first diagnostic code for diabetes (type 1 diabetes or type 2 diabetes) was recorded between 01/01/2006-31/12/2013, with no diagnoses prior to this date. We used a validated algorithm to classify patients with T2DM based on diabetes codes, treatments, age, BMI and ethnicity.¹⁹ The application of this algorithm using CPRD data has been described previously.²⁰ The index date in the T2DM cohort was defined as the first diagnostic code within the study window.

Patients with T2DM were matched (individual matching for categorical variables and caliper matching for continuous variables) with up to five controls without diabetes on year of birth (± 2 years), sex, and general practice. Patients with T2DM without any matched controls were excluded (6.9%). Individuals with T2DM and controls without diabetes were required to

have at least 1 year prior registration within the practice. All participants were observed from the index date to the endpoint date, study end date (31/03/2015), practice's last data collection date, death, or transfer out of practice.

Figure 1 outlines the study populations included at each analytical phase. In phase 2, risk of incident major adverse cardiac events (MACE) associated with diabetes, individuals with a history of cardiovascular disease were excluded. In phase 3, management of risk factors in diabetes, all individuals diagnosed with type 2 diabetes (with or without a history of CVD) were included.

Cardiovascular Outcomes

The primary endpoint was the first record of the following major adverse cardiac events (MACE) after the diagnosis of diabetes, identified from primary care (Read codes), HES data (ICD-10 codes) or ONS death data (ICD-10 codes): myocardial infarction (MI), stroke and cardiovascular death. Our secondary endpoints were: 1) fatal and non-fatal MI and 2) fatal and non-fatal stroke.

Patient Demographics and Baseline Clinical Characteristics

Ethnicity was identified from primary care records using Read codes and through linkage with HES as described previously.²⁰ Deprivation data was defined using the Index of Multiple Deprivation (IMD) 2010 classification at the level of the patient's residential postcode; categorised into five quintiles: IMD 1 (least deprived) to IMD 5 (most deprived).

Baseline data for obesity, HbA1c, blood pressure, hypercholesterolaemia (elevated total and LDL cholesterol), chronic kidney disease (stage 3 and above), microalbuminuria and proteinuria were captured as the closest measure up to 6 months before and 3 months after the index date (diabetes diagnosis date or corresponding date for controls). Further details on the definitions of these variables are provided in the Supplemental Methods. Cardiovascular disease

(including MI, coronary heart disease, stroke, transient ischaemic attack, peripheral vascular disease and cardiac arrest), neuropathy and retinopathy were defined using Read codes, up to the index date. Smoking status (current, former or never) was defined according to the closest recording before the index date.

Recorded HbA1c, blood pressure and cholesterol measurements were used to define risk factor control at baseline (further details are provided in the Supplemental Methods).

Patient Management Variables

To examine management in people with diabetes, we considered the frequency of risk factor checks, consultations with a healthcare professional within primary care, interventions offered and prescriptions for relevant medications. Risk factor observations included HbA1c tests, blood pressure checks, lipid checks, BMI measured and smoking cessation discussions recorded.

Consultations were defined into two main categories: face-to-face interactions and telephone interactions with a healthcare professional. Interventions offered were classified into diet intervention, exercise intervention, structured education and bariatric surgery. Drug prescriptions included diabetes therapies, antihypertensive agents, lipid-lowering therapies and antiplatelet agents.

Patient management variables were assessed at yearly intervals after the diabetes diagnosis date (index date) until patients' exit from study (end of follow-up). These data were summarised for the following time periods: year 1 (up to 3 months prior to and 12 months after the index date), years 2-3, years 4-5 and years 6-7. When patients had multiple measures recorded for biological variables within the time periods, the mean value was taken.

Management variables were stratified and assessed by time-varying CVD status (with /without CVD during each follow-up time period).

Minimum Standard of Care Indicators for Diabetes

Nine standards of care were considered based on QOF indicators for diabetes management in general practice between 2006 and 2013.^{21,22} The minimum standard of care indicators included: recording of BMI, HbA1c and blood pressure in the previous 15 months; testing for eGFR/serum creatinine and microalbuminuria in the previous 15 months; HbA1c, blood pressure and total cholesterol levels below specific targets in the previous 15 months; and treatment for microalbuminuria/proteinuria.

The indicators were assessed during the first 15 months of each follow-up time band following the diagnosis of diabetes (years 2-3, years 4-5 and years 6-7), in accordance with the QOF standards assessment period.



Statistical Analysis

Comparisons with T2DM and controls were sex-stratified for all analyses. In phase 1 of the study, baseline characteristics were summarised using mean (SD) and proportions as appropriate and comparisons by sex analysed using t-tests or chi-squared tests.

For phase 2, individuals with a history of cardiovascular disease at baseline were excluded. Stratified Cox proportional hazards models, accounting for the matched pairs (up to 1:5 case control ratio) by allowing for distinct underlying hazard functions for each matched set (stratum), estimated sex-specific hazard ratios (HR) for the primary and secondary outcomes in people with type 2 diabetes compared to controls without diabetes. Four models were constructed: 1) unadjusted, 2) adjusted for baseline calendar year, age, general practice, ethnicity, and deprivation, 3) additional adjustments for baseline smoking, obesity, hypertension, hypercholesterolaemia and Charlson Comorbidity Index (excluding diabetes and cardiovascular conditions; see the Supplemental Methods and Supplemental Table 1 for further details) and 4)

adjustment for time-varying risk factors to capture intervention-related changes; smoking, obesity, hypertension, hypercholesterolaemia and raised HbA1c ($>7\%$ [53mmol/mol]). As additional covariates were adjusted for in the Cox models, inclusion of the matching factors in the models was required. The two-fold fully conditional specification algorithm for multiple imputation was used to impute longitudinal measurements for obesity, hypertension, hypercholesterolaemia and raised HbA1c ($>7\%$ [53 mmol/mol]); further details in the Supplemental Methods. The ratio of hazard ratios between women (DM vs. Non-DM) and men (DM vs. Non-DM) were calculated to estimate excess risk for CVD in women who developed diabetes compared to men who developed diabetes. The age-specific influence of diabetes on incident MACE events in women and men was estimated using unadjusted and multivariable-adjusted Cox models stratified by age of onset of diabetes (<50 , $50\text{-}60$, $60\text{-}70$, ≥ 70 years of age). As a sensitivity analysis, we compared risk estimates for diabetes diagnoses between an earlier and later time period (2007-2010 vs 2011-2013) within the study (further details in the Supplemental Material) and performed the unadjusted analysis on a prevalent type 2 diabetes cohort.

In phase 3, within the diabetes cohort alone, including those with and without prevalent CVD, management variables were summarised as percentages or age-adjusted rates and multiple logistic regression models assessed sex differences in attainment of standard of care indicators within follow-up time bands. As a sensitivity analysis, specific care indicators were stratified by CVD and age (details provided in the Supplemental Material).

Time with poor control was calculated as the time from the first risk factor measurement above a specified threshold until either: 1) the first subsequent measurement below the threshold, 2) a change of drug regimen for the specific risk factor, or 3) end of follow-up; whichever came

first. For all drug therapies, the change in drug regimen was defined as the addition of a new drug to the current regimen and for diabetes medication this included adding insulin or switching to insulin. For each risk factor, sex-stratified cumulative incidence plots were constructed for the time from the risk factor level being above the cut-off to the time of drug intensification. The logrank test was used to determine if the probability of drug intensification occurring at any time point was significantly different in women and men; with a P-value<0.05 indicating a significant difference.

Finally, in patients with T2DM, we assessed sex differences in times to drug intensification after risk factor levels exceed specified thresholds.

Analyses were performed using Stata 15.1 (StataCorp LP, College Station, TX).



Results

Phase 1: The cohort comprised of 79,985 patients with incident T2DM (44.3% women) and 386,547 matched controls (44.8% women) with a mean \pm SD follow-up of 3.6 ± 2.4 years and 3.5 ± 2.4 years, respectively. Participant characteristics at baseline are presented in Table 1. At

baseline, women with T2DM were 2-3 years older; more likely to be obese, have hypercholesterolaemia and chronic kidney disease than men with T2DM. Men with T2DM were more likely to be current smokers and have higher HbA1c, hypertension, and diabetes-related microvascular and macrovascular complications than women with T2DM. For both men and women with T2DM, those without CVD at the time of diabetes diagnosis had a worse risk factor profile than those with CVD, with a greater propensity for poorly-controlled HbA1c, hypertension and hypercholesterolaemia (Supplemental Table 2). Women with CVD at baseline

were approximately 4 years older than men with CVD and were more likely to have lower HbA1c levels, but higher cholesterol and established kidney disease (Supplemental Table 2).

Phase 2: During follow-up, MACE events occurred in 9,806 people with diabetes (12.3% overall; 11.6% of women and 12.8% of men) and 30,226 people without diabetes (7.8% overall; 7.4% of women and 8.1% of men); Supplemental Table 3. In individuals without a previous history of cardiovascular disease, incident MACE events occurred in 4,564 people with diabetes (7.2% overall; 7.0% of women and 7.3% of men) and 11,665 people without diabetes (4.2% overall; 4.1% of women and 4.3% of men); Supplemental Table 3. The estimated hazard ratio of experiencing an incident MACE event associated with diabetes, after adjusting for baseline factors (non-modifiable and modifiable), was 1.23 (95% CI 1.16-1.32) for women and 1.17 (1.11-1.23) for men, leading to a non-significant excess risk in women (relative risk ratio 1.05 [95% CI 0.97-1.14]); Supplemental Table 4. After further adjusting for intervention-related changes in the modifiable risk factors in time-varying covariate-adjusted models, there remained no significant excess risk for MACE events in women compared to men (risk ratio: 1.07 [95% CI 0.98-1.17]); Supplemental Table 4 and Figure 2. Similar findings were observed when stratified by year of T2DM diagnosis (Supplemental Tables 5 and 6).

We examined the interaction between ethnicity and gender on CVD risk, which was not significant (not shown). An inverse association between age of onset of diabetes and risk of incident MACE events in women and men was observed, with the highest risk in those diagnosed with type 2 diabetes aged 50 or younger; HR 2.83 (95% CI 1.86-4.30) in women and HR 2.18 (95% CI 1.73-2.74) in men (Supplemental Table 7). The magnitude of the excess risk for MACE events in women compared to men was similar across all age bands, except in those

aged over 70 where this attenuated; however, we did not identify any significant sex disparities in CVD risk within age groups (with the exception of those diagnosed with T2DM aged 60-70).

Phase 3: Within the diabetes cohort (with/without prevalent CVD at baseline and during follow-up), we assessed rates of risk factor checks and consultations, the proportions with risk factor levels above target levels and proportions prescribed various medications for abnormal risk factors in patients at specific time points from diagnosis (Supplemental Table 8).

Management in men and women was broadly similar with some notable exceptions: a) compared to men, women had better glycaemic control; b) were more likely to be obese; c) have hypertensive end organ damage; and d) hypercholesterolaemia; but e) were less likely to be prescribed statin medication, despite having more frequent healthcare contacts.



Men and women without CVD at baseline or diagnosed during follow-up were consistently more likely to be obese, have poorer glycaemic control, hypertension, hypercholesterolaemia, and substantially lower prescribing of antihypertensive agents, antiplatelets and lipid-lowering medications than those with CVD (Supplemental Tables 9 and 10). Within patients without CVD, sex differences were observed with women more likely to have hypercholesterolaemia but with fewer prescriptions for lipid-lowering medications than men (Supplemental Table 10). In those with CVD at diagnosis or diagnosed during follow-up, the proportion of women receiving statins, antiplatelet medications and the majority of antihypertensive drugs (with the exception of ARIIBs and diuretics) was lower compared to men (Supplemental Table 9).

Performance against nine minimum care standards was assessed at different time intervals from the diabetes diagnosis (Supplemental Table 11). The proportion of women and men meeting each standard of care were comparable with a few exceptions in keeping with the

above analysis: a) women were less likely than men to have a total cholesterol ≤ 5 mmol/l; and b) were less likely to be prescribed ACE inhibitors in the presence of proteinuria or microalbuminuria (Supplemental Table 11); c) women were also less likely than men to be prescribed statins (Supplemental Table 12). Sex differences in achieved cholesterol levels and treatment with statins were more obvious in those with prevalent CVD compared to those without CVD (Supplemental Tables 11 and 12) and especially in younger patients (Supplemental Table 12).

Finally, in patients with T2DM, we assessed sex differences in times to drug intensification after risk factor levels exceed specified thresholds. These data indicated only modest sex differences in times to drug intensification (Figure 3; Supplemental Table 13): a) women with hypertension taking 0 or 1 antihypertensive agents were treated up to 1 month earlier than men on the same drug regimen. However, this modest early effect was not reflected in the probability of treatment intensification over 7 years (Supplemental Table 13) or when considering all hypertensive patients over the entire follow-up period (Figure 3); b) women with hypercholesterolemia and CVD were 10% less likely to be prescribed lipid lowering medication (Supplemental Table 13); c) there were no sex-related differences in the intensification of treatment for hyperglycaemia (Figure 3 and Supplemental Table 13).

Discussion

In contrast to findings from earlier studies, in this large contemporary primary care-based cohort study in England, we found that women who developed T2DM did not have a significantly higher relative increase in their risk for CVD than men who develop T2DM, before or after adjusting for non-modifiable and modifiable risk factors. However, some important sex

differences in the management of risk factors were observed. From onset of diabetes and in the subsequent years, compared to men with T2DM, women with T2DM had better glycaemic control but were more likely to have obesity, hypercholesterolaemia and hypertension and less likely to be prescribed lipid-lowering medication and ACE inhibitors, especially if they had CVD. In the T2DM subgroup, those without CVD at baseline or throughout follow-up consistently had worse risk factor control than those with CVD but had lower prescribing of antihypertensive agents, antiplatelets and lipid-lowering medications. In both subgroups with and without CVD, women were less likely to receive antiplatelet medications than men.

Prior studies of sex disparities in CVD risk associated with developing type 2 diabetes

Prior meta-analyses have shown that after developing diabetes, the increase in risk for fatal coronary heart disease, stroke or other atherosclerotic death was higher for women than men - with significant ratios of relative risks: 1.46 (95% CI: 1.14-1.88) for fatal coronary heart disease;⁵ 1.44 (1.27-1.63) for incident coronary heart disease;³ 1.27 (1.10-1.46) for stroke⁴; and 1.43 (1.27-1.61) for all fatal atherosclerotic disease.⁶ Although these meta-analyses included a large number of observational studies (n=37-68),³⁻⁶ these cohorts covered a much earlier era (approximate data collection: 1981-1995³, 1983-1997⁴, 1980-1992⁵, and 1985-2002⁶) when there may have been less emphasis on CVD risk reduction in clinical practice. Of the most recent CVD risk estimates from an English cohort, women were reported to have a higher risk for myocardial infarction after developing diabetes than men but there were no sex differences for other cardiovascular outcomes.²³

One potential explanation for these changing findings over time may be that less emphasis was placed on CVD risk in women with diabetes than in men.²⁴⁻²⁶ Our study uses contemporary data reflecting very recent clinical practice in the England where the quality and

equity of care may have been positively influenced by recent UK management guidelines¹⁶ and the QOF, a pay-for-performance initiative standardising service improvements in primary care.¹³

We observed that the risk of MACE was approximately 40% higher in people with T2DM compared to the general population (Figure 2), whereas prior studies have indicated a 2-3-fold higher risk associated with diabetes.³⁻⁶ The lower relative risks observed in our study may result from differences in the study populations. We identified community-based patients with incident type 2 diabetes undergoing contemporary CVD risk management who are likely to have lower CVD risks than many described in the prior literature.³⁻⁶ For example, prior studies included: a) people from ethnic groups with high CVD risk (e.g. Pima Indians and Pacific Islanders including Melanesian and Indian Fijians); b) those with prevalent diabetes patients; c) younger populations (<50 years) in whom relative risks associated with diabetes may be higher as indicated in Supplemental Table 7; and d) higher risk people from outside of primary care settings. As a sensitivity analysis, we performed an unadjusted analysis on a prevalent T2DM cohort (Supplemental Table 14). Compared to people without diabetes, the hazard ratios for MACE, MI and stroke events in the prevalent cohort were numerically higher for both women and men than in the incident cohort. However, the ratio of risks between women and men with type 2 diabetes were comparable and were not statistically different.

Sex disparities in risk factors

Historically, it has been thought that men with diabetes were diagnosed at an earlier age, were treated more actively, and were more likely to achieve recommended risk factor levels compared to women with diabetes.^{11,27} The UK National Diabetes Audit of nearly 2 million people studied between 2012 and 2013, showed that 58% of women and 62% of men received recommended

care processes, and that 34% of women and 37% of men achieved treatment targets for HbA1c, blood pressure and cholesterol.²⁸

In our cohort, men were diagnosed about 2.6 years earlier than women and generally CVD risk factor management was worse in women compared to men, with the exception of glycaemic control. It is known that at the diagnosis of type 2 diabetes, women have higher levels of BMI than men.⁷ The higher BMI levels in women could have a role in causing endothelial dysfunction, hypertension, dyslipidaemia and abnormalities in fibrinolysis and thrombosis that contribute to CVD risk.^{8,29,30}

Sex disparities in prescribing

The most notable gender disparities in prescribing were in relation to treatment with statins, ACE inhibitors and aspirin and we showed that these differences were only in part explained by avoidance of these medications in pre-menopausal women, in accordance with recommended guidelines (Supplemental Table 12).^{31,32} As those aged <50 accounted for only 17% of the total population of women at baseline, this should not have heavily impacted on the disparities we observed between men and women. Furthermore, the probability of lipid-lowering therapy initiation and escalation in those with hypercholesterolaemia was significantly lower in women, particularly so in those with CVD, a finding which has been observed previously.¹¹ The explanation behind lower prescribing in women with CVD than men with CVD is difficult to determine from these data and may be multifaceted. Potential explanations include: sex-related prescribing biases in physicians, sex-related differences in symptoms caused by coronary heart disease, or sex-related differences in patient attitudes and beliefs about their health status and requirement for medications. Further research is needed to better understand these findings.

Strengths and limitations

This study has several important strengths: First, we undertook a large retrospective population-based study using primary care data linked to hospital and mortality records allowing us to assess gender-related differences in CVD events, mortality, consultations and risk factor management associated with type 2 diabetes. Second, we used an incident cohort, which reflects contemporary practice and avoids the distorting influences of survival bias present in a prevalent cohort. Third, there were sufficient numbers of events to exclude clinically significant CVD risk differences between men and women developing diabetes and we were able to make meaningful comparisons of CVD risk factor management for up to 7 years following diagnosis.

We acknowledge some limitations: First, there was a relatively high proportion of missing data in non-diabetic controls for a number of CVD risk factors, along with missing data in the diabetes group; however we addressed this by performing multiple imputation using a number of clinical characteristics to provide appropriate estimates within these populations. The proportion of missing data was similar in men and women with or without diabetes. Therefore, this should not have heavily influenced estimates of CVD risk differences in men and women with diabetes. Furthermore, in accordance with previous observational evidence, an attenuation in the effect of diabetes with age on CVD risk was observed in both men and women (Supplemental Table 7) providing further reassurance of the robustness of this data.^{33–35} Second, our cohort, constructed with individuals with newly-diagnosed type 2 diabetes between 2006 and 2013, may limit comparisons with prior work that included individuals with prevalent diabetes. An incident cohort was sought as UK-wide changes to improve diabetes care were introduced over 2004–6 through the Quality and Outcomes Framework (QOF); therefore, prevalent diabetes diagnosed prior to this time could have distorted our findings. Furthermore, there are important

issues around survival bias with prevalent cases. It is a strength that our incident cohort reflects contemporary clinical management practice. Third, cohort characteristics and more active management of CVD risk in our contemporary cohort may explain the lower CVD risk associated with diabetes compared to more historical reports as described above. Fourth, the analyses based on patients assessed at fixed times following diagnosis (Supplemental Tables 8, 9 and 10) do not account for deaths and dropouts; however, loss to follow-up is unlikely to be strongly gender-related. Furthermore, data on CVD management was limited for years 6-7 years post-diagnosis due to the smaller sample size with longer follow-up; the average duration of follow-up was 3.6 ± 2.4 years, explained by CVD and mortality events, patients entering the cohort later and cohort attrition. Finally, the analysis is based on data from English general practices and so generalisation to other healthcare systems may be limited. The sex disparity in cholesterol control and lipid-lowering prescribing observed in this study have been observed in other diabetes populations;^{36–38} however, comprehensive longitudinal studies of all aspects of type 2 diabetes care in different countries are needed to evaluate the full extent of any current sex disparities in treatment and management.

Clinical implications

Reassuringly, we showed that the previously reported gender disparities in CVD risk associated with T2DM are not evident in contemporary English general practice. However, the observed gender biases in risk factor management highlight the need for closer adherence to clinical guidance for drug therapy, continued routine surveillance for gender-related prescribing biases and possibly greater uptake of professional-based interventions in the community to support the provision of equitable care.^{39,40} Particular attention is required for high-CVD risk women without established CVD, who may not be receive optimal preventative care.

Conclusions

Whilst there is clear improvement in the relative risks for CVD events, sex disparities in the management of CVD risk factors should prompt renewed efforts to improve the standard and equity of diabetes care for women and men with diabetes.

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Table 1. Baseline clinical characteristics of patients with incident type 2 diabetes (T2DM) and matched controls without diabetes

	T2DM (N=79,985)		Controls (N=386,547)	
	Women	Men	Women	Men
n, %	35,396 (44.3)	44,589 (55.8)	172,994 (44.8)	213,553 (55.3)
Age, years	63.9±14.3	61.3±13.0	63.7±14.4	60.8±13.0
Ethnicity				
White	28,090 (79.4)	34,251 (77.4)	127,344 (73.6)	145,259 (68.0)
South Asian	1,544 (4.4)	1,792 (4.0)	2,960 (1.7)	3,357 (1.6)
Black	784 (2.2)	748 (1.7)	2,226 (1.3)	2,223 (1.0)
Other	400 (1.1)	507 (1.1)	1,545 (0.9)	1,8012 (0.8)
Unknown	4,578 (12.9)	7,021 (15.8)	38,919 (22.5)	60,913 (28.5)
Deprivation				
IMD 1 (least deprived)	6,330 (17.9)	8,810 (19.8)	37,354 (21.6)	48,7132 (22.8)
IMD 2	7,624 (21.5)	10,225 (22.9)	40,447 (23.4)	50,231 (23.5)
IMD 3	7,063 (20.0)	9,039 (20.3)	34,934 (20.2)	42,807 (20.1)
IMD 4	7,614 (21.5)	8,961 (20.1)	33,356 (19.3)	39,8665 (18.7)
IMD 5 (most deprived)	6,708 (19.0)	7,510 (16.8)	26,698 (15.4)	31,667 (14.8)
Unknown	57 (0.2)	44 (0.1)	205 (0.1)	269 (0.1)
Obese	18,517 (52.3)	22,011 (49.4)	17,815 (10.3)	18,758 (8.8)
Smoking				
Current	11,203 (31.7)	20,883 (46.8)	45,309(26.2)	72,517 (34.0)
Ex-smoker	9,923 (28.0)	11,564 (25.9)	47,009 (27.2)	59,265 (27.8)
Never	1,992 (5.6)	1,468 (3.3)	9,489 (5.5)	7,669 (3.6)
Unknown	12,278 (34.7)	10,674 (23.9)	71,187 (41.2)	74,102 (34.7)
HbA1c >7% (53mmol/mol)	15,819 (44.7)	21,867 (49.0)	-	-
HbA1c >8% (64mmol/mol)	8,844 (25.0)	13,599 (30.5)	-	-
BP>140/80 mmHg	10,683 (30.2)	14,199 (31.8)	18,142 (10.5)	18,768 (8.8)
BP>130/80 mmHg	15,577 (44.0)	19,638 (44.0)	26,636 (15.4)	26,737 (12.5)
<i>with target organ damage</i>	4,537 (12.8)	3,660 (8.2)	9,393 (5.4)	6,856 (3.2)
Hypercholesterolaemia*	8,973 (25.4)	10,244 (23.0)	5,357 (3.1)	5,958 (2.8)
Risk factors in control †				
1 Risk factor in control	14,617 (41.3)	17,531 (39.3)	154,999 (89.6)	195,919 (91.7)
2 Risk factors in control	4,815 (13.6)	5,813 (13.0)	17,693 (10.2)	16,861 (7.9)
3 Risk factors in control	503 (1.4)	820 (1.8)	302 (0.2)	773 (0.4)
Cardiovascular Disease				
Coronary heart disease	3,910 (11.1)	7,506 (16.8)	10,767 (6.2)	20,096 (9.4)
Cerebrovascular disease	2,175 (6.1)	2,737 (6.1)	7,563 (4.3)	9,369 (4.4)
Peripheral vascular disease	946 (2.7)	1,808 (4.1)	2,631 (1.5)	4,813 (2.3)
Chronic kidney disease	7,921 (22.4)	5,974 (13.4)	21,238 (12.3)	16,162 (7.6)
Microalbuminuria or proteinuria	3,416 (9.7)	5,923 (13.3)	2,735 (1.6)	3,726 (1.7)

Peripheral neuropathy	343 (1.0)	527 (1.2)	565 (0.3)	789 (0.4)
Retinopathy	1,278 (3.6)	1,825 (4.1)	25 (0.01)	23 (0.01)
History of pregnancy	10,312 (29.1)	-	50,399 (29.1)	-
Hormone-replacement therapy (current use) ‡	451 (1.3)	-	3,079 (1.8)	-
Oral contraceptives (current use) ‡	397 (1.1)	-	1,380 (0.8)	-

Data presented as N (%) or mean±SD

* total cholesterol>4mmol/L or LDL cholesterol>2mmol/L

† HbA1c <7% (53mmol/mol); BP < 130/80mmHg; lipids: total cholesterol<4mmol/L or LDL cholesterol<2mmol/L

‡ Current use defined as prescriptions up to 90 days prior to index date

% missing data in T2DM: Obesity 12.2% (women 12.8%, men 11.7%), HbA1c 17.8% (women 17.8%, men 17.8%), Blood Pressure 29.5% (women 28.7%, men 30.1%), Hypercholesterolaemia 65.8% (women 66.7%, men 65.1%), Microalbuminuria/Proteinuria 46.1% (women 46.7%, men 45.5%).

% missing data in Controls: Obesity 66.5% (women 63.4%, men 69.0%), HbA1c 97.8% (women 97.7%, men 97.9%), Blood Pressure 77.5% (women 74.5%, men 79.9%), Hypercholesterolaemia 96.3% (women 96.4%, men 96.2%), Microalbuminuria/Proteinuria 92.4% (women 91.4%, men 93.2%)



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Figure Legends

Figure 1. Definition of cohorts across study phases

Figure 2. Unadjusted and multivariable-adjusted hazard ratios for incident CVD comparing people with and without T2DM by sex, and ratio of risk (RRR) for women relative to men

Adjusted for age, ethnicity, deprivation, general practice, calendar year, baseline: smoking, obesity, hypertension, hypercholesterolaemia, comorbidities and time-varying: smoking, obesity, hypertension, hypercholesterolaemia, raised HbA1c.



Ratio of relative risks (RRR) greater than 1 indicates an excess risk for incident CVD in women who developed diabetes compared to men who developed diabetes.

CVD indicates cardiovascular disease; T2DM, type 2 diabetes; MACE, major adverse cardiac events; MI, myocardial infarction; HR, hazard ratio; CI, confidence interval.

Figure 3. Comparison of the proportion of men and women undergoing intensification of drug regimens in relation to the time that their risk factors (HbA1c, BP, lipids) were above threshold values: A) HbA1c >7% (53mmol/mol); B) BP >140/80 mmHg in patients with prevalent CVD, C) LDL-cholesterol >2 mmol/L or total cholesterol >4 mmol/L in patients with prevalent CVD, D) LDL-cholesterol >2 mmol/L or total cholesterol >4 mmol/L in patients without prevalent CVD

BP indicates blood pressure; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; CVD, cardiovascular disease.

Phase 1: Clinical characteristics of type 2 diabetes patients and matched controls

Individuals with incident type 2 diabetes (N=79,985)

Inclusion criteria:

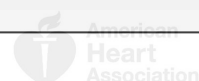
- i.* First diagnosis of diabetes (type 1 diabetes or type 2 diabetes) recorded between 1 January 2006 and 31 December 2013 (index date). Algorithm applied to classify those with type 2 patients
- ii.* Must have at least 1 year prior registration at current practice
- iii.* Practice and individual's data meeting CPRD "up to standard" criteria for research
- iv.* Eligible for linkage to Hospital Episode Statistics (HES), Office for National Statistics mortality data and deprivation data

Individuals without diabetes (N=386,547)

Inclusion criteria:

- i.* No record of any type of diabetes
- ii.* Must have at least 1 year prior registration at current practice
- iii.* Practice and individual's data meeting CPRD "up to standard" criteria for research
- iv.* Eligible for linkage to Hospital Episode Statistics (HES), Office for National Statistics mortality data and deprivation data

People with diabetes were matched to up to 5 people without diabetes (N=386,547) on year of birth (± 2 years), sex, and general practice.



Phase 2: Major cardiovascular event (MACE) risk associated with diabetes, by sex

Individuals with prevalent cardiovascular disease were excluded

Type 2 diabetes (N=63,718; 29,348 (46.1%) women and 34,370 (53.9%) men) and Controls (N=277,176; 130,524 (47.1%) women and 146,652 (52.9%) men)

MACE defined as fatal/non-fatal myocardial infarction, fatal/non-fatal stroke and cardiovascular death.

Individuals observed from the index date to the MACE endpoint date, study end date (31 March 2015), practice's last data collection date, death, or transfer out of practice. Maximum follow-up of 9 years.

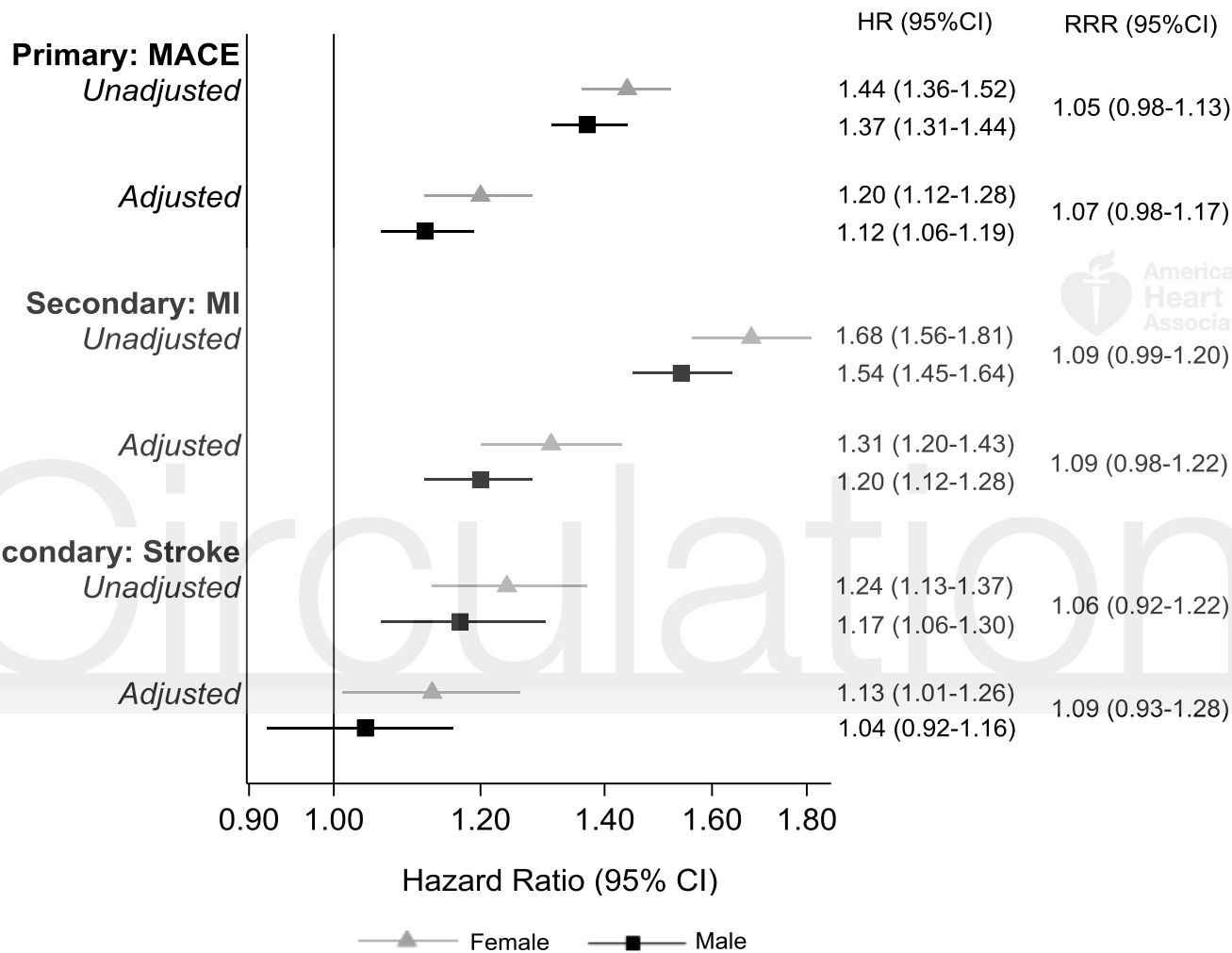
Phase 3: Sex associated cardiovascular risk factor management in type 2 diabetes

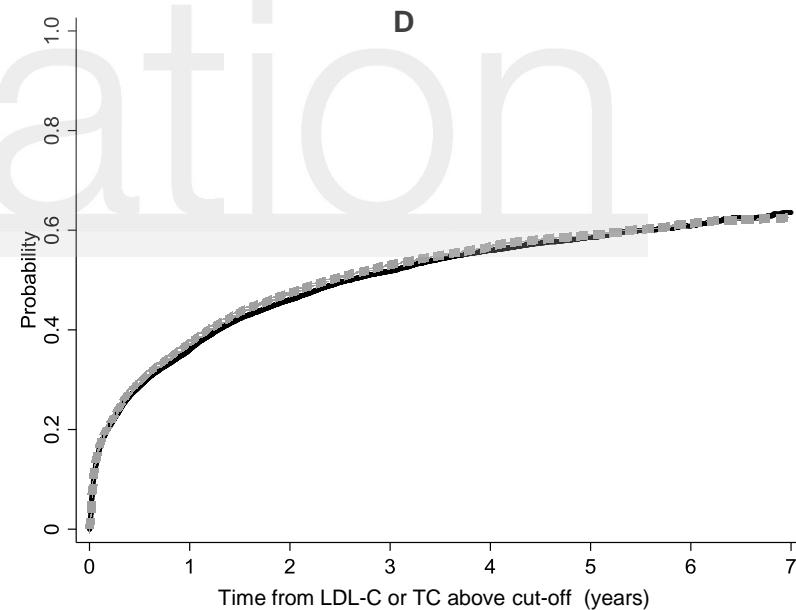
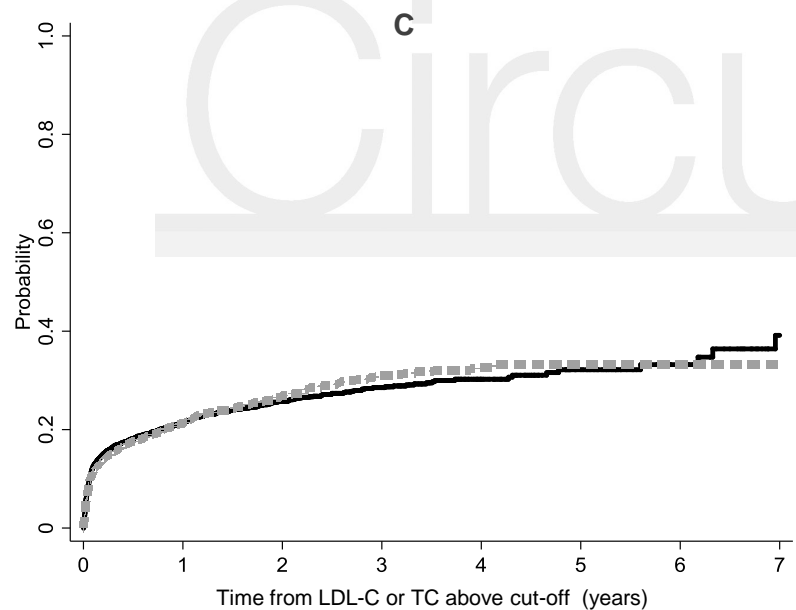
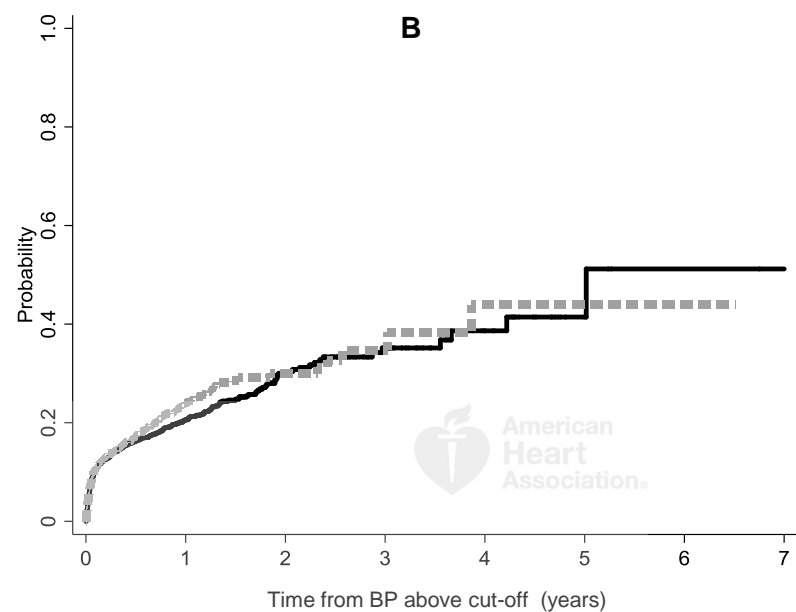
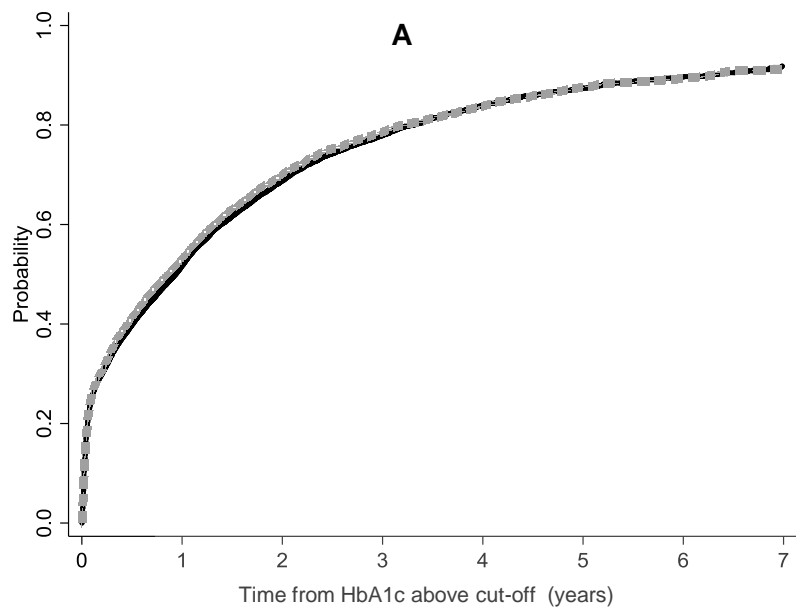
Individuals with prevalent cardiovascular disease were included

**Type 2 diabetes (N=79,985)
Women (n=35,396; 44.3%); Men (n=44,589; 55.8%)**

Risk Factors, clinical characteristics and patient management data captured during follow-up time bands after diabetes diagnosis; Year 1 (-3 months to +12 months), Years 2-3, Years 4-5, Years 6-7. Follow-up time captured during Phase 2.

Minimum Standard of Care Indicators for diabetes captured during follow-up time bands from Years 2-3.





— Male - - - - Female